APPENDIX C

Interfering Smith and Engelhardt Claims Corresponding to Count 2

Proposed Count 2	Smith Claim 41	Engelhardt Claim 1769	Why the Claims Interfere
A method for determining the sequence of a polynucleotide which comprises: *or* A process for determining the sequence of a nucleic acid of interest comprising the steps of:	A method for determining the sequence of a polynucleotide which comprises:	A process for determining the sequence of a nucleic acid of interest comprising the steps of:	Smith Claim 41 anticipates or renders obvious Engelhardt Claim 1769 and vice versa because a "method for determining the sequence of a polynucleotide" (Smith Claim 41) is merely an alternative way of stating a "process for determining the sequence of a nucleic acid of interest" (Engelhardt Claim 1769). Thus, there is no patentable distinction between these two claim limitations.
providing polynucleotide fragments generated by a polynucleotide sequencing technique, which are tagged with chromophores or fluorophores, wherein the fragments from one or more of the four sequencing reactions A, C, G or T are distinguishable from fragments of the other reactions by their spectral characteristics;	providing polynucleotide fragments generated by a polynucleotide sequencing technique, which are tagged with chromophores or fluorophores, wherein the fragments from one or more of the four sequencing reactions A, C, G or T are distinguishable from fragments of the other reactions by their spectral characteristics;	providing at least one nucleic acid of interest; generating detectable non-radioactively labeled nucleic acid fragments complementary to said nucleic acid of interest or a portion thereof, wherein said fragments have been labeled by incorporation of one or more nucleoside triphosphates comprising different fluorescent indicators;	Smith Claim 41 anticipates or renders obvious Engelhardt Claim 1769 and vice versa for several reasons: First, Smith Claim 41 and Engelhardt Claim 1769 set forth the same inventive concept, namely, using different indicators (e.g., fluorescent labels) for labeling nucleotides employed in the sequencing reactions. Unlike Smith Claim 41, Engelhardt Claim 1769 does not explicitly recite "fragments from one or more of the four sequencing reactions A, C, G or T [which] are distinguishable from fragments of the other reactions by their spectral characteristics." However,

Proposed Count 2	Smith Claim 41	Engelhardt Claim 1769	Why the Claims Interfere
or providing at least one nucleic acid of interest; generating detectable non-radioactively labeled nucleic acid fragments complementary to said nucleic acid of interest or a portion thereof, wherein said fragments have been labeled by incorporation of one or more nucleoside triphosphates comprising different fluorescent indicators;			Engelhardt Claim 1769 is directed to determining the sequence of a nucleic acid of interest, which necessarily involves using fragments from one or more of the four sequencing reactions A, C, G or T. Second, Engelhardt Claim 1769 recites that the fragments are labeled with *different* indicator molecules. The term "different" connotes that the labels are not the same, i.e., that they are distinguishable from one another. Further, although Engelhardt Claim 1769 does not recite that the fragments are distinguishable from other fragments "by their spectral characteristics" (as Smith Claim 41 does), that limitation is inherent in Engelhardt Claim 1769's recitation that the fragments are labeled with nucleoside triphosphates comprising different fluorescent indicators. "Spectral characteristics" are simply characteristics of light emission, such as intensity or color.[16] The nucleic acids which have incorporated the "nucleoside triphosphates comprising different fluorescent indicators" (as recited in Engelhardt Claim 1769) can be distinguished from one another

[16] A "spectral characteristic" is "The relation between wavelength and some other variable, such as between wavelength and emitted radiant power...." *McGraw-Hill Dictionary of Scientific and Technical Terms*, 5th Ed. (1994). Wavelength is another word for color. Color is defined as a "general term that refers to the wavelength composition of light...." *Id.*

Proposed Count 2	Smith Claim 41	Engelhardt Claim 1769	Why the Claims Interfere
			based on their color or other spectral characteristics. Indeed, as disclosed in the Engelhardt Application, labeled nucleic acids can be detected or distinguished via their "colors," "fluorescent illumination," "light microscope visualization," "fluorescent light microscopy", "imaging very low levels of fluorescent light," or "using currently available image intensifiers or systems composed of lasers and photomultipliers."[17] Finally, during prosecution of the Smith patent, Smith equated detectability based on spectral characteristics with detectability based on color.[18] Smith stated that the tags were "inherently detectable" "simply by virtue of its color (i.e., light absorption), which emission from a fluorophore-labeled oligonucleotide is detectable upon illumination with light having a wavelength

[17] *See* Application, p. 32, 2nd ¶ ("fluorescent illumination"), p. 36, 3rd ¶ ("colored precipitates permits light microscope visualization," "fluorescent light microscopy"), p. 37, 2nd ¶ ("Detecting and/or imaging very low levels of fluorescent light is possible using currently available image intensifiers or systems composed of lasers and photomultipliers....Using systems of this kind or flow systems in which the cells or parts of cells flow past a laser beam, one can obtain sensitivity increases for fluorescent material....This increase is sufficient to detect the fluorescence of single copy genes."), p. 47, 1st ¶ (reproduced above), p. 48, 1st ¶ (reproduced above).

[18] Smith's discussions are relevant to the proper interpretation of Count 2 because Count 2 incorporates Smith Claim 41.

[19] Amendment dated February 26, 1999, Appl. No.: 08/484,340

[20] Office Action dated April 13, 1994, App. No.: 07/898,019

Proposed Count 2	Smith Claim 41	Engelhardt Claim 1769	Why the Claims Interfere
			appropriate for the particular fluorophore."[19] Indeed, the Examiner in the Smith prosecution seemed to agree that detecting a fluorophore and observing its spectral characteristics are one and the same thing. For instance, in an Office Action, the Examiner equated "fluorescence" with "spectral characteristics."[20]
resolving the fragments by electrophoresis; *or* subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments; and	resolving the fragments by electrophoresis;	subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments; and	Smith Claim 41 anticipates or renders obvious Engelhardt Claim 1769 and vice versa because a "resolving the fragments by electrophoresis" (Smith Claim 41) is merely an alternative way of stating a "subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments" (Engelhardt Claim 1769). Thus, there is no patentable distinction between these two claim limitations.
detecting the fragments as they are being resolved by means of the spectral characteristics of the chromophores or fluorophores, and thereby determining the polynucleotide sequence based on the polynucleotide fragments detected.	detecting the fragments as they are being resolved by means of the spectral characteristics of the chromophores or fluorophores, and thereby determining the polynucleotide sequence based on the polynucleotide fragments detected.	detecting said separated or resolved fragments by means of said different fluorescent indicators, to determine the sequence of said nucleic acid of interest.	Smith Claim 41 anticipates or renders obvious Engelhardt Claim 1769 and vice versa because a "detecting the fragments... by means of the spectral characteristics of the chromophores or fluorophores, and thereby determining the polynucleotide sequence" (Smith Claim 1) is merely an alternative way of stating a "detecting said separated or resolved fragments by means of the fluorescent indicators, to determine the sequence of said nucleic acid of interest"

Proposed Count 2	Smith Claim 41	Engelhardt Claim 1769	Why the Claims Interfere
detected. *or* detecting said separated or resolved fragments by means of said different fluorescent indicators, to determine the sequence of said nucleic acid of interest.			(Engelhardt Claim 1769). There is no patentable distinction between these two claim limitations.

Proposed Count 2	Smith Claim 28	Engelhardt Claim 1796	Why the Claims Interfere
A method for determining the sequence of a polynucleotide which comprises: *or* A process for determining the sequence of a nucleic acid of interest comprising the steps of:	A method for determining the sequence of a polynucleotide which comprises:	A process for determining the sequence of a nucleic acid of interest comprising:	Smith Claim 28 anticipates or renders obvious Engelhardt Claim 1796 and vice versa because a "method for determining the sequence of a polynucleotide" (Smith Claim 28) is merely an alternative way of stating a "process for determining the sequence of a nucleic acid of interest" (Engelhardt Claim 1796). Thus, there is no patentable distinction between these two claim limitations.
providing polynucleotide fragments generated by a polynucleotide sequencing technique, which are tagged with chromophores or fluorophores, wherein the fragments from one or more of the four sequencing reactions A, C, G or T are distinguishable from fragments of the other reactions by their spectral characteristics; *or* providing at least one nucleic acid of interest; generating detectable non-	providing polynucleotide fragments tagged with chromophores or fluorophores, wherein the chromophores or fluorophores are distinguishable from others by their spectral characteristics;	providing or generating detectable non-radioactively labeled nucleic acid fragments comprising: (a) a sequence complementary to said nucleic acid of interest or a portion thereof, and (b) different fluorescent labels covalently attached, directly or through a linkage group, to said fragments;	Smith Claim 28 anticipates or renders obvious Engelhardt Claim 1796 and vice versa because "providing polynucleotide fragments tagged with chromophores or fluorophores... distinguishable from others by their spectral characteristics" (Smith Claim 28) is an alternative way of stating "providing or generating detectable non-radioactively labeled nucleic acid fragments comprising... different fluorescent labels covalently attached... to said fragments" (Engelhardt Claim 1796). Thus, there is no patentable distinction between these two claim limitations.

Proposed Count 2	Smith Claim 28	Engelhardt Claim 1796	Why the Claims Interfere
radioactively labeled nucleic acid fragments complementary to said nucleic acid of interest or a portion thereof, wherein said fragments have been labeled by incorporation of one or more nucleoside triphosphates comprising different fluorescent indicators;			
resolving the fragments by electrophoresis; *or* subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments; and	resolving the polynucleotide fragments by electrophoresis; and	subjecting said labeled fragments to a sequencing gel to separate or resolve said labeled fragments;	Smith Claim 28 anticipates or renders obvious Engelhardt Claim 1796 and vice versa because there is no practical distinction between "resolving the polynucleotide fragments by electrophoresis" (Smith Claim 28) and "subjecting said labeled fragments to a sequencing gel to separate or resolve said labeled fragments" (Engelhardt Claim 1796). Thus, there is no patentable distinction between these two claim limitations.
detecting the fragments as they are being resolved by means of the spectral characteristics of the chromophores or fluorophores, and thereby determining the	detecting the resolved fragments by means of the chromophores or fluorophores, and thereby determining the sequence based on the polynucleotide fragments detected.	detecting non-radioactively said separated or resolved fragments by means of said attached different fluorescent labels; and determining the sequence of said nucleic acid of interest from said detected	Smith Claim 28 anticipates or renders obvious Engelhardt Claim 1796 and vice versa because "detecting the resolved fragments by means of the chromophores or fluorophores, and thereby determining the sequence" (Smith Claim 28) is an alternative way of stating "detecting non-radioactively

Proposed Count 2	Smith Claim 28	Engelhardt Claim 1796	Why the Claims Interfere
polynucleotide sequence based on the polynucleotide fragments detected. *or* detecting said separated or resolved fragments by means of said different fluorescent indicators, to determine the sequence of said nucleic acid of interest.		fragments.	said separated or resolved fragments by means of said attached different fluorescent labels; and determining the sequence" (Engelhardt Claim 1796). No patentable distinction exists between these two claim limitations. Furthermore, as explained in the text above, both Smith Claim 28 and Engelhardt Claim 1796 correspond to Count 2 because the count renders obvious both claims. Although Engelhardt Claim 1796 does not recite that the fragments are sequenced "by means of the spectral characteristics of the chromophores or fluorophores," this is inherent in the claim, which requires that the "fluorescent labels" be "different," i.e., distinguishable from one another.